

# THE PROBABILITY OF EXTINCTION OF ISAV IN ONE AND TWO PATCHES

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**ABSTRACT.** Deterministic models to study the dynamics of infectious diseases have been an effective tool for prediction of the persistence of infection. The basic reproduction number  $\mathcal{R}_0$  has been shown to be a threshold in such models with  $\mathcal{R}_0 > 1$  a sufficient condition for persistence of the disease. It is also a sufficient condition for the ability of the pathogen to invade. However, in the case of invasion, infectious classes are initially present in small quantities. In this case, random fluctuations drive the dynamics of the system. Several deterministic models of Infectious Salmon Anemia virus (ISAv) in one and two patches are presented and recast as stochastic models to capture the effects of random fluctuations on disease outbreak. The probability of outbreak in these systems is analyzed via the analysis of its complement, the probability of disease extinction. It has been shown that under certain assumptions the probability of extinction can be accurately approximated by multitype branching processes. The probability of extinction is approximated in each model for a variety of initial conditions using branching process approximation and numerical simulation. The single patch deterministic model is modified to include a more realistic force of infection. The equilibria of the modified system are determined along with its basic reproduction number,  $\mathcal{R}_0$ . Furthermore, an analogous stochastic model is proposed and the probability of extinction is determined. For branching process approximation to be accurate it has long been known that the number of susceptible individuals at the disease free equilibrium (DFE) must be sufficiently large. This critical size is estimated for the one patch system for different transition rates by comparison of the branching process approximation and Monte Carlo simulation as the population at the DFE varies.

## 1. INTRODUCTION

Infectious salmon anemia virus (ISAv), is the virus which causes infectious salmon anemia (ISA) with 15 to 100% accumulated mortality over the course of a several months long infection in a farm environment [7]. It is found in all large salmon-producing countries including Norway, Scotland, Ireland, Canada, the United States, and Chile [26]. ISAv is transmitted among finfish horizontally by passive movement of infected seawater [21] and via direct contact with excretions or secretions of infected individuals. Salmon farms consist of a collection of net cages placed in open body of water. It is known that the location of salmon farms among wild salmon migratory routes in British Columbia raises the level of sea lice infection [18]. In this article we recall earlier results [22] in the analysis of deterministic Susceptible-Infected-Virus (SIV) models of ISAv outbreak in one and two patches pertaining to the invasion of the virus. For each of these previously studied models, a companion continuous time Markov chain (CTMC) model is introduced and as well as a multitype Galton-Watson branching process. Finally, the deterministic model of infection in one patch is modified to reflect a Monod-like force of infection (*f.o.i.*). This allows

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for the force of infection to be alternately driven by the infected class or the free virus or a combination of the two, depending on their relative concentrations. It simplifies to the classical Monod *f.o.i.* for a special choice of parameters. Corresponding CTMC and multitype branching process models are also developed. For the branching process to be an accurate approximation of the CTMC, the disease free number of susceptible individuals must be sufficiently large. The critical number of susceptibles is estimated and compared for the original one patch system and the modified one patch system numerically for a single set of parameter values.

It is natural to study the effect of introducing a pathogen into an otherwise naive ecosystem. Deterministic models predict that as long as  $\mathcal{R}_0 > 1$ , the pathogen is able to invade and persist. However, when the disease free population of susceptible individuals is large and the amount of pathogen is small or when the total population is small the dynamics of the system are affected by random fluctuations. Deterministic models do not take this randomness into account and a CTMC model is introduced to capture these effects. We refer to the case when a small amount of pathogen is introduced to an entirely susceptible population as disease emergence. The critical question is: does the introduction of the disease lead to outbreak or extinction of the disease? In the context of randomness we cannot expect as certain a prediction as we have in the deterministic setting, but we can determine the likelihood of outbreak or extinction. As in the deterministic case, there is an absorbing subset of the state space associated to the extinction of the disease. Therefore, the question becomes what is the likelihood of hitting this subspace. While there is a theoretical solution to the hitting probability problem for the CTMC, when the state space is large or infinite finding this solution for a specific CTMC is often impractical. Assuming the number of individuals in non-infectious classes does not change from the initial value, the CTMC model is characterized by the transitions among the infectious classes. Supposing all transitions are independent, this new Markov chain can be cast as a Galton-Watson or Bienaymé-Galton-Watson branching process (BGWbp). BGWbp theory originated with Galton and Watson to study the extinction of surnames and later extended to multitype BGWbp's by Sevast'yanov, Kolmogorov, Dmitriev and Everett and Ulam to study fission reactions [13]. The application of branching processes to epidemics goes back to Whittle's approximation of disease extinction in a susceptible-infected-recovered (SIR) model with constant total population [28].

In the application of BGWbp theory to epidemics the probability of extinction is related to the probability of all infectious classes becoming extinct upon the introduction of one individual of a single infectious class. This is the complement of invasion of the infectious class when introduced at the disease free equilibrium in the deterministic system. It is therefore not surprising that Whittle found that when  $\mathcal{R}_0 > 1$  the probability of extinction given the introduction of  $i$  infected individuals is  $(1/\mathcal{R}_0)^i$  [1, 28]. Allen and van den Driessche made the relationship between the multitype BGWbp and the associated deterministic system precise in their Threshold Theorem [2]. Allen and Lahodny consider the probability of extinction in a multi-patch Susceptible-Infected-Susceptible (SIS) model where there is migration in both the susceptible and infected classes and infected individuals experience additional disease induced mortality [19]. In this article, we study the branching process approximation of a two patch model with infected and free virus infectious classes in each patch and only the virus can migrate between patches.

The two patch deterministic system admits an invariant subsystem corresponding to one patch in isolation. This deterministic one patch system was previously studied [22]. Results are recalled and the associated CTMC and multitype BGWbp models are presented and probability of extinction determined. David Bean, a biologist in the Greater Atlantic

Regional Fisheries Office suggested in conversation that infected fish may cause most new infections in the initial stages of an outbreak while free virus may drive the *f.o.i.* later, once the concentration of free virus is larger due to viral shedding, before finally saturating. The one patch model is modified to reflect this possibility by replacing the *f.o.i.* with a variant on the Monod *f.o.i.* that allows for the trade-off between infected fish and free virus causing new infections based on their relative population size.

In order to employ a BGWbp approximation of disease emergence the underlying system must satisfy two assumptions: *i*) All transitions must be independent; and *ii*) the disease free number of susceptible individuals must be sufficiently large. The first assumption is restrictive for biological application, but required for the branching process to be suitable. The second assumption is not required in order to make a branching process approximation, but is necessary for the approximation to be accurate. While it has long been known that the initial populations of susceptible individuals must satisfy critical size in order to be accurately approximated in this way [3, 28], the question of how large is sufficiently large remains open. In order to gauge the accuracy of the branching process approximation, the probability of extinction in the CTMC which allows for transitions in the susceptible class is approximated numerically. Numerical results are then compared alongside the branching process approximation. We perform this comparison for the original one patch model and the modified one patch model across a range of initial population sizes in order to estimate the critical size and compare between models.

This article is organized as follows: We recall a two patch SIV model of ISAV and introduce its stochastic CTMC and BGWbp counterparts in Section 2. In that same section a prediction for the probability of extinction of the virus is made when the disease free number of susceptibles is sufficiently large and its accuracy tested numerically. Similar analysis and predictions for the model in only one patch are performed first for the one patch system with mass action *f.o.i.* in Section 3 and the system with Monod *f.o.i.* in Section 4. In Section 5, the critical size of the disease free population of susceptible fish is estimated for the original one patch model, the model with Monod *f.o.i.* and the original model with a lower rate of mortality for infected fish. Section 6 contains some conclusions that can be drawn from these results.

## 2. TWO PATCH MODEL OF ISAV

**2.1. Deterministic SIV-SIV model.** In [22], a two patch SIV model is proposed to study the dynamics of an ISAV infection. The two patches are coupled solely via diffusion of the virus. Birth and death rates are patch dependent and are denoted by a subscript associated to the patch. All other parameters are patch independent. This yields the following system:

$$(1) \quad \begin{cases} \dot{S}_1 &= S_1(\beta_1 - \mu_1 S_1) - S(I_1 + V_1) \\ \dot{I}_1 &= S_1(I_1 + V_1) - \alpha I_1 \\ \dot{V}_1 &= k(V_2 - V_1) - \omega V_1 + \delta I_1 \\ \dot{S}_2 &= S_2(\beta_2 - \mu_2 S_2) - S_2(I_2 + V_2) \\ \dot{I}_2 &= S_2(I_2 + V_2) - \alpha I_2 \\ \dot{V}_2 &= k(V_1 - V_2) - \omega V_2 + \delta I_2. \end{cases}$$

where  $\beta_1, \beta_2$  are the patch specific birth rates of susceptible fish,  $\mu_1, \mu_2$  the their patch specific, density dependent mortality rates,  $\alpha$  is the mortality rate of infected fish,  $\delta$  is the rate at which infected fish shed the virus into the environment,  $\omega$  is the rate at which it clears from the environment and  $k$  is the rate of viral diffusion.

System (1) admits 7 equilibria in total. Four equilibria corresponding to the case where the virus is absent:  $(0,0,0,0,0,0)$ ,  $(\bar{S}_1, 0, 0, 0, 0, 0)$ ,  $(0, 0, 0, \bar{S}_2, 0, 0)$ , DFE =  $(\bar{S}_1, 0, 0, \bar{S}_2, 0, 0)$ . Let

$$\mathcal{R}_1^0 = \frac{(\omega(2k + \omega) + \delta(k + \omega))\beta_1}{\alpha\omega(2k + \omega)\mu_1} \quad \mathcal{R}_2^0 = \frac{(\omega(2k + \omega) + \delta(k + \omega))\beta_2}{\alpha\omega(2k + \omega)\mu_2}$$

be the patch specific reproduction numbers corresponding to host fish only in patch one or only in patch two, respectively. Then system (1) admits two additional equilibria corresponding to the case where there are host fish only in patch one or only in patch two:  $(S_1', I_1', V_1', 0, 0, V_2') \iff \mathcal{R}_1^0 > 1$  and  $(0, 0, V_1^*, S_2^*, I_2^*, V_2^*) \iff \mathcal{R}_2^0 > 1$ . The basic reproduction number for system (1) is given by

$$\mathcal{R}_0 = \frac{1}{2}(\mathcal{R}_1^0 + \mathcal{R}_2^0 + \sqrt{(\mathcal{R}_1^0 - \mathcal{R}_2^0)^2 + 4\bar{S}_1\bar{S}_2C^2}),$$

where  $C = \frac{\delta k}{\alpha\omega(2k + \omega)}$ . From [22] we have that DFE is globally asymptotically stable (*g.a.s.*) if and only if  $\mathcal{R}_0 \leq 1$ . If  $\mathcal{R}_0 > 1$ , then the DFE is unstable and the virus invades and persists when introduced. In fact, the subset of the boundary associated to the extinction of the virus is a uniform strong repeller whenever  $\mathcal{R}_0 > 1$ . If, in addition, the following symmetric conditions are met,

$$\mathcal{R}_1^0 > \frac{\mu_2}{\mu_1}Q(\mathcal{R}_2^0 - 1) \quad \text{and} \quad \mathcal{R}_2^0 > \frac{\mu_1}{\mu_2}Q(\mathcal{R}_1^0 - 1),$$

where  $Q = \frac{\delta k}{\omega(2k + \omega) + \delta(k + \omega)}$ , then there exists a unique positive endemic equilibrium.

**2.2. Stochastic SIV-SIV model.** From the preceeding deterministic model we consider the CTMC  $\mathbf{X}(t) = (S_1(t), I_1(t), V_1(t), S_2(t), I_2(t), V_2(t))$  with the infinitesimal transition probability to state  $j$  from state  $i$  is given by

$$p_{i,j}(\Delta t) = \mathbb{P}\{\mathbf{X}(t + \Delta t) = j \mid \mathbf{X}(t) = i\} = \sigma(i, j)\Delta t + o(\Delta t),$$

where  $\sigma(i, j)$  is the exponential rate associated to the transition from state  $i$  to state  $j$  and can be found in Table 1. Assuming that  $S_1(t) \equiv \bar{S}_1$ ,  $S_2(t) \equiv \bar{S}_2$  and that all transitions associated to the remaining infectious classes are independent we may construct a branching process to approximate the CTMC near the DFE. Let  $e_i$  be the standard basis vector with 1

Description	Transition	rate $\sigma(i, j)$
Birth of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 + 1, I_1, V_1, S_2, I_2, V_2)$	$\beta_1 S_1$
Death of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 - 1, I_1, V_1, S_2, I_2, V_2)$	$\mu_1 S_1^2$
Infection of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 - 1, I_1 + 1, V_1, S_2, I_2, V_2)$	$S_1(I_1 + V_1)$
Death of $I_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1 - 1, V_1, S_2, I_2, V_2)$	$\alpha I_1$
Shedding of $V_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1 + 1, S_2, I_2, V_2)$	$\delta I_1$
Clearance of $V_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1 - 1, S_2, I_2, V_2)$	$\omega V_1$
Diffusion of $V_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1 - 1, S_2, I_2, V_2 + 1)$	$k V_1$
Birth of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 + 1, I_1, V_1, S_2, I_2, V_2)$	$\beta_2 S_2$
Death of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 - 1, I_1, V_1, S_2, I_2, V_2)$	$\mu_2 S_2^2$
Infection of $S_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1 - 1, I_1 + 1, V_1, S_2, I_2, V_2)$	$S_2(I_2 + V_2)$
Death of $I_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1 - 1, V_1, S_2, I_2, V_2)$	$\alpha I_2$
Shedding of $V_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1 + 1, S_2, I_2, V_2)$	$\delta I_2$
Clearance of $V_1$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1 - 1, S_2, I_2, V_2)$	$\omega V_2$
Diffusion of $V_2$	$(S_1, I_1, V_1, S_2, I_2, V_2) \mapsto (S_1, I_1, V_1, S_2, I_2, V_2 + 1)$	$k V_2$

TABLE 1. State transitions and rates for the CTMC SIV-SIV model.

in the  $i^{th}$  coordinate and 0 in all other coordinates. The probability generating function for the branching process is given by

$$\mathbf{F}(\mathbf{u}) = \begin{pmatrix} f_1(\mathbf{u}) \\ f_2(\mathbf{u}) \\ f_3(\mathbf{u}) \\ f_4(\mathbf{u}) \end{pmatrix},$$

when  $(I_1(0), V_1(0), I_2(0), V_2(0)) = e_1$ , the pgf for  $I_1$  is

$$f_1(u_1, u_2, u_3, u_4) = \frac{\alpha + \delta u_1 u_2 + \bar{S}_1 u_1^2}{\alpha + \delta + \bar{S}_1},$$

when  $(I_1(0), V_1(0), I_2(0), V_2(0)) = e_2$ , the pgf for  $V_1$  is

$$f_2(u_1, u_2, u_3, u_4) = \frac{\omega + k u_4 + \bar{S}_1 u_1 u_2}{\omega + k + \bar{S}_1},$$

when  $(I_1(0), V_1(0), I_2(0), V_2(0)) = e_3$ , the pgf for  $I_2$  is

$$f_3(u_1, u_2, u_3, u_4) = \frac{\alpha + \delta u_3 u_4 + \bar{S}_2 u_3^2}{\alpha + \delta + \bar{S}_2},$$

and when  $(I_1(0), V_1(0), I_2(0), V_2(0)) = e_4$ , the pgf for  $V_2$  is

$$f_4(u_1, u_2, u_3, u_4) = \frac{\omega + k u_2 + \bar{S}_2 u_3 u_4}{\omega + k + \bar{S}_2}.$$

The matrix of expectations is given by

$$\mathbb{M} = \begin{bmatrix} \frac{\delta + 2\bar{S}_1}{\alpha + \delta + \bar{S}_1} & \frac{\delta}{\alpha + \delta + \bar{S}_1} & 0 & 0 \\ \frac{\bar{S}_1}{\omega + k + \bar{S}_1} & \frac{\bar{S}_1}{\omega + k + \bar{S}_1} & 0 & \frac{k}{\omega + k + \bar{S}_1} \\ 0 & 0 & \frac{\delta + 2\bar{S}_2}{\alpha + \delta + \bar{S}_2} & \frac{\delta}{\alpha + \delta + \bar{S}_2} \\ \frac{k}{\omega + k + \bar{S}_2} & 0 & \frac{\bar{S}_1}{\omega + k + \bar{S}_1} & \frac{\bar{S}_1}{\omega + k + \bar{S}_1} \end{bmatrix}$$

It is easily verified that this multitype branching process is positively regular and not singular. From Theorem 7.1 [Harris 1963] the Threshold Theorem [Allen, van den Driessche 2013] it follows that

$$\mathbb{P}_0 = q_1^{I_1(0)} q_2^{V_1(0)} q_3^{I_2(0)} q_4^{V_2(0)}$$

with  $\mathbf{q} = \mathbf{1}$  if  $\mathcal{R}_0 \leq 1$  and  $\mathbf{q} \in (0, 1)$  if  $\mathcal{R}_0 > 1$ .

**2.3. Numerical example.** For the purpose of illustrating the accuracy of the branching process approximation we consider the parameter vector  $(\beta_1 = 12, \mu_1 = 0.05, \beta_2 = 10, \mu_2 = 0.04, \alpha = 3.3, \delta = 1.3, \omega = 4, k = 3)$ . Then  $\bar{S}_1 = 240, \bar{S}_2 = 250, \mathcal{R}_1^0 \approx 89, \mathcal{R}_2^0 \approx 93, \mathcal{R}_0 \approx 98 \gg 1$ . The endemic equilibrium is located numerically as the root of the nonlinear system (1) and is given by  $(S_1 = 2.53, I_1 = 9.09, V_1 = 2.78, S_2 = 2.45, I_2 = 7.34, V_2 = 2.56)$ . The vector  $\mathbf{q}$  of extinction probabilities was determined iterating the pgf initially at the origin. The summary and statistics of numerical simulation is provide beside branching process approximation results in Table 2.

$I_1(0)$	$V_1(0)$	$I_2(0)$	$V_2(0)$	$\mathbb{P}_0$	$\mathbb{P}_0^{10,000}$	Variance of $\mathbb{P}_0^{10,000}$	$\mathbb{P}_0^{1,000,000}$
1	0	0	0	0.0137	0.0122	$1.56 \times 10^{-6}$	0.0136
0	1	0	0	0.0166	0.0185	$1.48 \times 10^{-6}$	0.0167
0	0	1	0	0.0131	0.0132	$1.36 \times 10^{-6}$	0.0131
0	0	0	1	0.0160	0.128	$2.01 \times 10^{-6}$	0.0160

TABLE 2. Probability of extinction of the virus from the initial condition  $(\bar{S}, i_0, v_0, w_0)$  with the parameter vector  $(\beta_1 = 12, \mu_1 = 0.05, \beta_2 = 10, \mu_2 = 0.04, \alpha = 3.3, \delta = 1.3, \omega = 4, k = 3)$  approximated by branching process and numerically over 10,000 and 1,000,000 realizations. The variance is computed over 100 calculations of numerical approximations made over 10,000 realizations.

### 3. ONE PATCH MODEL

**3.1. Deterministic SIV model.** When there is no diffusion, i.e.  $k = 0$ , then each patch of the two patch system form invariant SIV subsystems given by:

$$(2) \quad \begin{cases} \dot{S} &= S(\beta - \mu S) - S f(I, V) \\ \dot{I} &= S f(I, V) - \alpha I \\ \dot{V} &= -\omega V + \delta I. \end{cases}$$

where  $f(I, V) = f_1(I, V) = (I + V)$ ,  $\beta$  is the birth rate of susceptible fish,  $\mu$  the mortality rates of susceptible fish,  $\alpha$  the mortality rate of infected fish,  $\omega$  is the rate of viral clearing and  $\delta$  is the rate of viral shedding. All of these parameters are assumed to be positive.

The system admits equilibria  $(0,0,0)$ , the disease free equilibrium (DFE) at  $(\bar{S}, 0, 0)$ . The basic reproduction number is,

$$(3) \quad \mathcal{R}_0 = \frac{(\delta + \omega)\beta}{\alpha\omega\mu}.$$

When  $\mathcal{R}_0 > 1$  the system also admits a unique positive endemic equilibrium.  $\mathcal{R}_0 = 1$  is also a threshold for the dynamics of the system. If  $\mathcal{R}_0 \leq 1$ , then the DFE is *g.a.s.*. If  $\mathcal{R}_0 > 1$ , then the DFE is unstable and the virus invades and persists when introduced. The largest invariant subset of the boundary is a uniform strong repeller when  $\mathcal{R}_0 > 1$ .

**3.2. Stochastic SIV model.** The CTMC model  $\mathbf{X}(t) = (S(t), I(t), V(t))$  associated to system (2) with  $f(I, V) = f_1(I, V)$  is characterized by the exponential transition rates given in Table 3.

Description	Transition	rate $\sigma(i, j)$
Birth of $S$	$(S, I, V) \mapsto (S + 1, I, V)$	$\beta S$
Death of $S$	$(S, I, V) \mapsto (S - 1, I, V)$	$\mu S^2$
Infection	$(S, I, V) \mapsto (S - 1, I + 1, V)$	$S(I + V)$
Death of $I$	$(S, I, V) \mapsto (S, I - 1, V)$	$\alpha I$
Shedding of $V$	$(S, I, V) \mapsto (S, I, V + 1)$	$\delta I$
Clearance of $V$	$(S, I, V) \mapsto (S, I, V - 1)$	$\omega V$

TABLE 3. State transitions and rates for the CTMC SIV model.

To estimate the probability of extinction of the virus we approximate the CTMC near the DFE. That is, we assume that  $S(t) \equiv \bar{S}$  and that all transition events related to  $(I(t), V(t))$  are independent. With these assumptions we can construct the probability-generating function (pgf) for the branching process approximation. Let  $I(0) = i_0$  and  $V(0) = v_0$ . We consider two initial conditions,  $(i_0, v_0) = (1, 0)$  and  $(i_0, v_0) = (0, 1)$ . From  $(1, 0)$  it is possible to transition to  $(0, 0)$ ,  $(1, 1)$  or  $(2, 0)$  with probabilities  $p_{00} = \frac{\alpha}{\alpha + \delta + \bar{S}}$ ,  $p_{11} = \frac{\delta}{\alpha + \delta + \bar{S}}$  and  $p_{20} = \frac{\bar{S}}{\alpha + \delta + \bar{S}}$ , respectively. From  $(0, 1)$  it is possible to transfer to  $(0, 0)$  or  $(1, 1)$  with probabilities  $p_{00} = \frac{\omega}{\omega + \bar{S}}$  and  $p_{11} = \frac{\bar{S}}{\omega + \bar{S}}$ , respectively. Together these yield the pgf

$$\mathbf{F}(u_1, u_2) = \begin{pmatrix} f_1(u_1, u_2) \\ f_2(u_1, u_2) \end{pmatrix} = \begin{pmatrix} \alpha + \delta u_1 u_2 + \bar{S} u_1^2 \\ \frac{\alpha + \delta + \bar{S}}{\omega + \bar{S} u_1 u_2} \\ \frac{\omega + \bar{S}}{\omega + \bar{S}} \end{pmatrix}.$$

Thus, the functions  $f_i$  for  $i = 1, 2$  are not simple and the matrix of expectations is given by

$$\mathbb{M} = \begin{bmatrix} \frac{\delta + 2\bar{S}}{\alpha + \delta + \bar{S}} & \frac{\delta}{\alpha + \delta + \bar{S}} \\ \frac{\bar{S}}{\omega + \bar{S}} & \frac{\bar{S}}{\omega + \bar{S}} \end{bmatrix},$$

is a positive irreducible matrix. Thus,  $\mathbb{M}$  is monotone and  $\lim_{n \rightarrow \infty} \mathbf{F}^n(\mathbf{u}) = \mathbf{q}$  in the compact unit interval. Then  $\mathbf{F}(\mathbf{q}) = \mathbf{q}$  or

$$(4) \quad \frac{\alpha + \delta q_1 q_2 + \bar{S} q_1^2}{\alpha + \delta + \bar{S}} = q_1$$

$$(5) \quad \frac{\omega + \bar{S} q_1 q_2}{\omega + \bar{S}} = q_2$$

Solving (4) and (5) for  $q_2$  and setting them equal yields the cubic equation

$$G(q_1) = a_0 q_1^3 + a_1 q_1^2 + a_2 q_1 + a_3,$$

with  $a_0 > 0$ ,  $a_3 < 0$  and  $G(1) = 0$ . By direct calculation it can be verified that

- $\text{sgn}(G'(1)) = \text{sgn}(1 - \mathcal{R}_0)$ ;
- $g(q_1) = \frac{G(q_1)}{(q_1 - 1)}$  has two positive real roots;
- $\mathcal{R}_0 = 1 \rightarrow G''(1) < 0$ .

Together, these imply that there is a unique root of  $G$  in  $(0, 1)$  if and only if  $\mathcal{R}_0 > 1$ . This root is given by with

$$(6) \quad q_1 = \frac{\alpha + \delta + \omega + \bar{S} - \sqrt{(\alpha - (\omega + \bar{S}))^2 + \delta(\delta + 2(\alpha + \omega + \bar{S}))}}{2\bar{S}}$$

From (5) we have that

$$(7) \quad q_2 = \frac{\omega}{\omega + \bar{S}(1 - q_1)}$$

so that  $0 < q_1 < 1$  implies  $0 < q_2 < 1$ . Then the probability of extinction of the virus

$$\mathbb{P}_0 = \lim_{t \rightarrow \infty} (\mathbf{Z}(t) = 0 \mid \mathbf{Z}(0) = (i_0, v_0)) = q_1^{i_0} q_2^{v_0},$$

where  $\mathbf{q} = \begin{pmatrix} q_1 \\ q_2 \end{pmatrix}$  satisfies  $\mathbf{F}(\mathbf{q}) = \mathbf{q}$  if and only if  $\mathcal{R}_0 > 1$ . Otherwise  $\mathbb{P}_0 = 1$ . This result combined with Theorem 7.1 of [Harris 1963] implies that the dominant eigenvalue of  $\mathbb{M}$ ,  $q > 1$  if and only if  $\mathcal{R}_0 > 1$ .

**3.3. Numerical example.** The following example provides numerical evidence of the accuracy of the branching process approximation. For the purpose of this example we consider the parameter vector given by  $(\beta = 12, \mu = 0.05, \alpha = 3.3, \delta = 1.3, \omega = 4)$ . This yields  $\mathcal{R}_0 \approx 96 \gg 1$ . The endemic equilibrium of the deterministic system is approximately  $(S = 2.49, I = 8.96, V = 2.91)$ . The probability of extinction of the virus, numerical  $\mathbb{P}_0^N$ , is estimated by taking the proportion of stochastic realizations in which the infectious classes hit zero before hitting an endemic level. This quantity is calculated over  $N$  realizations.  $\mathbb{P}_0^{10,000}$  is calculated 100 times to calculate the mean and variance of this quantity. Note that the mean is equivalent to determining  $\mathbb{P}_0$  numerically over 1,000,000 realizations. The initial condition  $S(0) = \frac{\beta}{\mu} = 240$ , the value at the disease free equilibrium. The initial values  $i_0$  and  $v_0$  can be found in Table 4 along with the relevant statistics.

#### 4. ONE PATCH MODEL WITH MONOD FORCE OF INFECTION

**4.1. Deterministic model.** The one patch model given by system (2) proposes a Michelis-Menton or mass action force of infection. It has been suggested that the *f.o.i.* may initially be driven by infected salmon encountering susceptible salmon when free virus is present at low levels at the outset of an exposure event. As more salmon become infected and shed

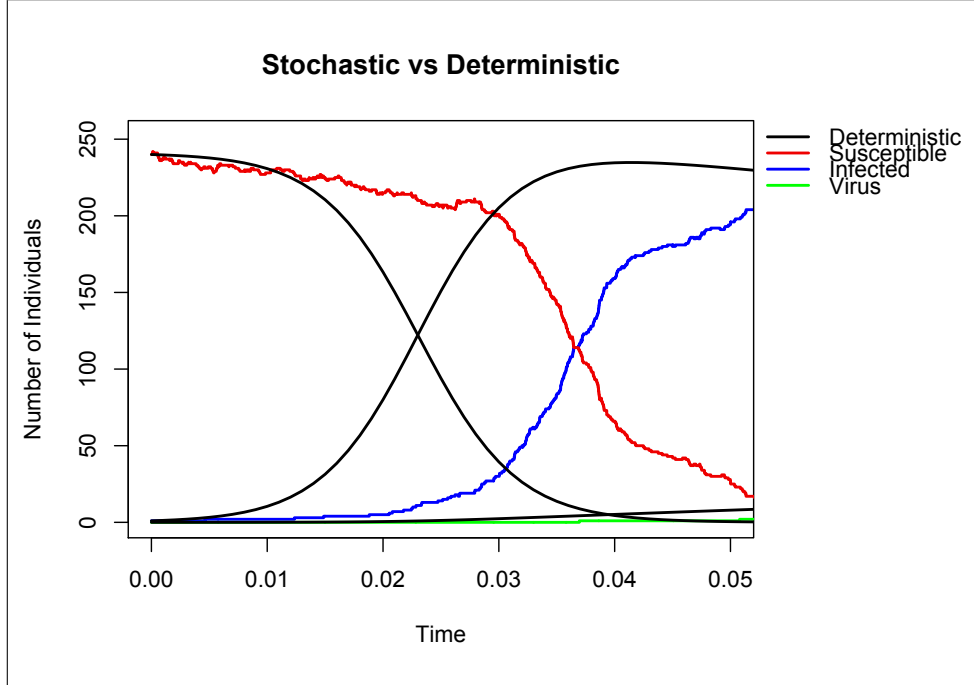


FIGURE 1. One realization of the Markov chain model compared to solution of the deterministic model. Both simulations take initial condition  $(S = 240, I = 1, V = 0)$  and parameter vector  $(\beta = 12, \mu = 0.05, \alpha = 3.3, \delta = 1.3, \omega = 4)$ .



$i_0$	$v_0$	$q_1^i q_2^{v_0}$	$\mathbb{P}_0^{10,000}$	Variance of $\mathbb{P}_0^{10,000}$	$\mathbb{P}_0^{1,000,000}$
1	0	0.0137	0.0136	$1.23 \times 10^{-6}$	0.0137
0	1	0.0166	0.0162	$1.81 \times 10^{-6}$	0.0167
1	1	0.0002	0.0002	$2.45 \times 10^{-8}$	0.0002

TABLE 4. Probability of extinction of the virus from the initial condition  $(\bar{S}, i_0, v_0)$  with the parameter vector  $(\beta = 12, \mu = 0.05, \alpha = 3.3, \delta = 1.3, \omega = 4)$  approximated by branching process and numerically over 10,000 and 1,000,000 realizations. The variance is computed over 100 calculations of numerical approximations made over 10,000 realizations.

more and more virus into the environment, the free virus may then drive the infection. To account for this we modify system (2) by considering  $f(I, V) = f_2(I, V)$  where

$$f_2(I, V) = \frac{m_1 I}{a_1 + I + V} + \frac{m_2 V}{a_2 + I + V}$$

Note that when  $m_1 = m_2$  and  $a_1 = a_2$ , the growth function  $\frac{m_1 I}{a_1 + I + V} + \frac{m_2 V}{a_2 + I + V}$  simplifies to the standard Monod growth for  $I + V$ . System (2) with  $f(I, V) = f_2(I, V)$  admits equilibria at  $\mathbf{0}$  and the DFE  $(\frac{\beta}{\mu}, 0, 0)$ . Following the next generation matrix approach [25, 6] the basic reproduction number is determined to be

$$(8) \quad \mathcal{R}_0 = \frac{m_1 a_2 + \frac{\delta}{\omega} m_2 a_1 \beta}{\alpha a_1 a_2 \mu}.$$

The endemic equilibrium is a root of the vector field. From  $\dot{V} = 0$  we have  $V' = \frac{\delta}{\omega} I'$ . Substituting into  $\dot{I} = 0$  yields  $S' = f_1(I')$ . Let  $f_2(I') = \frac{m_1 I'}{a_1 + (1 + \frac{\delta}{\omega}) I'}$  and  $f_3(I') = \frac{m_2 \frac{\delta}{\omega} I'}{a_2 + (1 + \frac{\delta}{\omega}) I'}$ . Then the nonnegative root of  $\dot{S} = 0$  is a root of the equation

$$(9) \quad \beta - \mu \alpha f_1(I') - f_2(I') - f_3(I') = 0.$$

Furthermore,  $f_1'(I'), f_2'(I'), f_3'(I') > 0$  and  $f_2(0) = f_3(0) = 0$ . Thus, (9) has a unique positive root if and only if  $f_1(0) < \beta \iff \mathcal{R}_0 > 1$ . Thus, there exists a unique positive endemic equilibrium if and only if  $\mathcal{R}_0 > 1$ . If  $\mathcal{R}_0 \leq 1$  then the DFE is *g.a.s.*. This system has the same dynamics on the boundary as the system with mass action *f.o.i.*. Using arguments similar to those in [22], it follows that system (2) with  $f(I, V) = f_2(I, V)$  is uniformly strongly persistent whenever  $\mathcal{R}_0 > 1$ .

**4.2. Stochastic model.** The CTMC model related to system (2) with  $f(I, V) = f_2(I, V)$  is characterized by the transitions and rates given in Table 5 Table 5. We approximate the

Description	Transition	rate $\sigma(i, j)$
Birth of $S$	$(S, I, V) \mapsto (S + 1, I, V)$	$\beta S$
Death of $S$	$(S, I, V) \mapsto (S - 1, I, V)$	$\mu S^2$
Infection	$(S, I, V) \mapsto (S - 1, I + 1, V)$	$S(\frac{m_1 I}{a_1 + I + V} + \frac{m_2 V}{a_2 + I + V})$
Death of $I$	$(S, I, V) \mapsto (S, I - 1, V)$	$\alpha I$
Shedding of $V$	$(S, I, V) \mapsto (S, I, V + 1)$	$\delta I$
Clearance of $V$	$(S, I, V) \mapsto (S, I, V - 1)$	$\omega V$

TABLE 5. State transitions and rates for the CTMC SIV model.

CTMC near the DFE using a branching process approximation with the pgf given by

$$\mathbf{F}(\mathbf{u}) = \begin{pmatrix} f_1(\mathbf{u}) \\ f_2(\mathbf{u}) \end{pmatrix} = \begin{pmatrix} \frac{\alpha + \delta u_1 u_2 + \bar{S} \frac{m_1}{a_1+1} u_1^2}{\alpha + \delta + \bar{S} \frac{m_1}{a_1+1}} \\ \frac{\omega + \bar{S} \frac{m_2}{a_2+1} u_1 u_2}{\omega + \bar{S} \frac{m_2}{a_2+1}} \end{pmatrix}.$$

The matrix of expectations is given by

$$\mathbb{M} = \begin{bmatrix} \frac{\delta + 2\bar{S} \frac{m_1}{a_1+1}}{\alpha + \delta + \bar{S} \frac{m_1}{a_1+1}} & \frac{\delta}{\alpha + \delta + \bar{S} \frac{m_1}{a_1+1}} \\ \frac{\bar{S} \frac{m_2}{a_2+1}}{\omega + \bar{S} \frac{m_2}{a_2+1}} & \frac{\bar{S} \frac{m_2}{a_2+1}}{\omega + \bar{S} \frac{m_2}{a_2+1}} \end{bmatrix}.$$

Clearly, the branching process is not singular and  $\mathbb{M}$  is a positive matrix. If the dominant eigenvalue of  $\mathbb{M}$  is greater than 1 (equivalently, if  $\mathcal{R}_0 > 1$ ) then there exists a unique  $\mathbf{q} \in \mathbb{R}^2$  such that  $\mathbf{F}(\mathbf{q}) = \mathbf{q}$  and  $\mathbb{P}_0 = q_1^{i_0} q_2^{v_0}$  where  $i_0 = I(0)$  and  $v_0 = V(0)$ . Let  $\Delta_1 = \frac{m_1}{a_1+1}$  and  $\Delta_2 = \frac{m_2}{a_2+1}$ . Following arguments similar to those used in section 3.2, if  $\mathbf{q} = (q_1, q_2)^T$  then  $q_1$  is also the root of a quadratic equation  $g(u) = au^2 + bu + c$ . Let  $\mathcal{D} = \frac{b^2 - 4ac}{\bar{S}^2}$ . Then

$$(10) \quad \mathcal{D} = (\alpha \Delta_2 - \Delta_1 (\bar{S} \Delta_2 + \omega))^2 + \delta \Delta_2^2 (\delta + 2\alpha + 2\bar{S} \Delta_1) + 2\delta \omega \Delta_1 \Delta_2 > 0$$

and

$$(11) \quad \mathbf{q} = \begin{pmatrix} q_1 \\ q_2 \end{pmatrix} = \begin{pmatrix} \frac{\alpha \Delta_2 + \delta \Delta_2 + \omega \Delta_1 + \bar{S} \Delta_1 \Delta_2 - \sqrt{\mathcal{D}}}{2\bar{S} \Delta_1 \Delta_2} \\ \frac{\omega}{\omega + \bar{S} \Delta_2 (1 - q_1)} \end{pmatrix}$$

**4.3. Numerical example.** For the purpose of example and to evaluate the accuracy of the branching process approximation to the CTMC near the DFE we fix the parameter vector ( $\beta = 12, \mu = 0.05, \alpha = 3.3, \omega = 4, \delta = 1.3, m_1 = 6, m_2 = 7.5, a_1 = 3, a_2 = 2$ ). This implies that  $\bar{S} = 240, \mathcal{R}_0 \approx 234 \gg 1$  and that the endemic equilibrium is approximately (113.83, 217.60, 70.72). The extinction probability predicted by the branching process approximation is compared with numerical results in Table 6.

## 5. CRITICAL SIZE OF DISEASE FREE POPULATION

The accuracy of the branching process approximation relies on its ability to capture the transitions that take place in the infectious classes. Extinction in the one patch CTMC model is equivalent to hitting a subset of the state space comprised of lattice points on the  $S$ -axis. Therefore, changes in the susceptible component of the state are only important to the calculation of the extinction probability in-so-far-as the transition probabilities in the infectious classes depend on  $S$ . If the susceptible class remained constant throughout the

$i_0$	$v_0$	$q_1^{i_0} q_2^{v_0}$	$\mathbb{P}_0^{1,000,000}$
1	0	0.0091	0.0090
0	1	0.0067	0.0067
1	1	0.0001	0.0001

TABLE 6. Probability of extinction of the virus from the initial condition  $(\bar{S}, i_0, v_0)$  with the parameter vector ( $\beta = 12, \mu = 0.05, \alpha = 3.3, \omega = 4, \delta = 1.3, m_1 = 6, m_2 = 7.5, a_1 = 3, a_2 = 2$ ) approximated by branching process and numerically over 1,000,000 realizations.

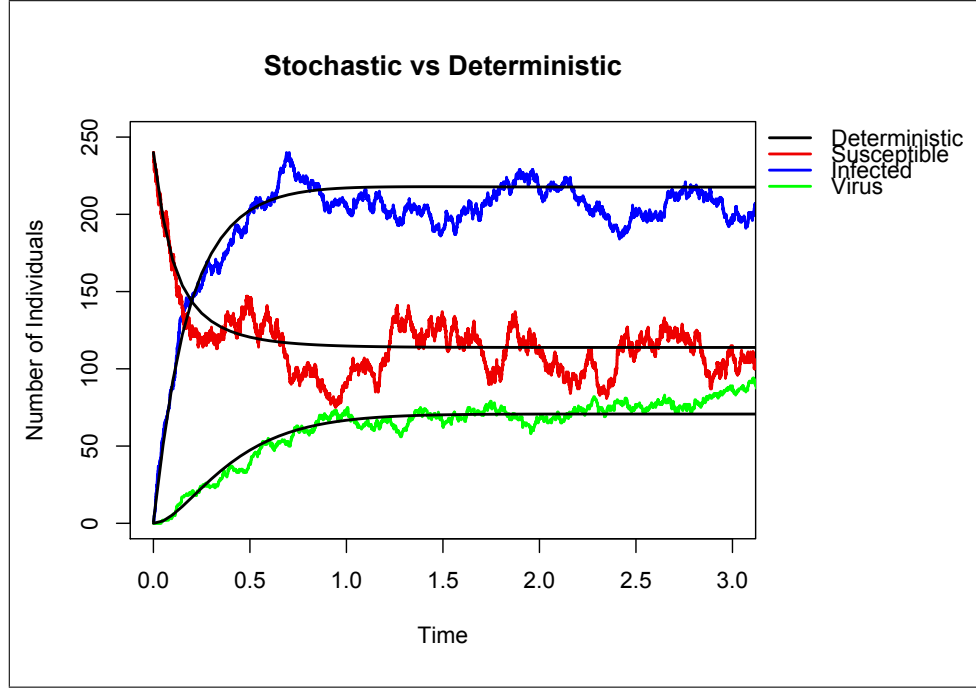


FIGURE 2. One realization of the Markov chain model compared to solution of the deterministic model. Both simulations take initial condition  $(S = 240, I = 1, V = 0)$  and parameter vector  $(\beta = 12, \mu = 0.05, \alpha = 3.3, \omega = 4, \delta = 1.3, m_1 = 6, m_2 = 7.5, a_1 = 3, a_2 = 2)$ .

evolution of the infectious classes prior to extinction, then the multitype branching process would have exactly the same transition probabilities as the CTMC. If the initial population of susceptible individuals is sufficiently large, then it will remain approximately constant throughout the evolution of the infectious classes and the multitype branching process will have approximately the same transition probabilities as the CTMC. At present, there is no analytical estimate of the critical size of the initial population. In this section, the critical size is approximated numerically for a range of initial population sizes for the single patch model. To illustrate how changes to the transition probabilities effect the critical population size, approximations are made for the system with mass action *f.o.i.* (Figure 3) and Monod *f.o.i.* (Figure 4) both with a high rate of mortality for infected fish. The critical size is also approximated for the system with mass action *f.o.i.* with a low rate of mortality for infected fish (Figure 5). The probability of extinction is estimated numerically and via multitype branching process approximation in the case that a single infected individual is introduced to the system (i.e.  $I(0) = 1, V(0) = 0$ ). The branching process approximation is a continuous function of the disease free number of susceptible fish and is given by (6) and (11) for the system with mass action and Monod *f.o.i.*, respectively. For purposes of simulations the density dependent mortality rate  $\mu$  is assumed to be 1 for simplicity. Under this assumption the disease free number of susceptible fish is equal to the birth rate  $\beta$ . For simulations with high mortality rate for infected fish,  $\alpha = 3.3$  and for low mortality  $\alpha = 1.5$ . The remaining parameters are fixed as reported in Section 4.3. That is  $\omega = 4, \delta = 1.3$  and when  $f(I, V) = f_2(I, V)$ ,  $m_1 = 6, m_2 = 7.5, a_1 = 3$ , and  $a_2 = 2$ . For the purpose of numerical simulations, the probability of extinction is estimated by the

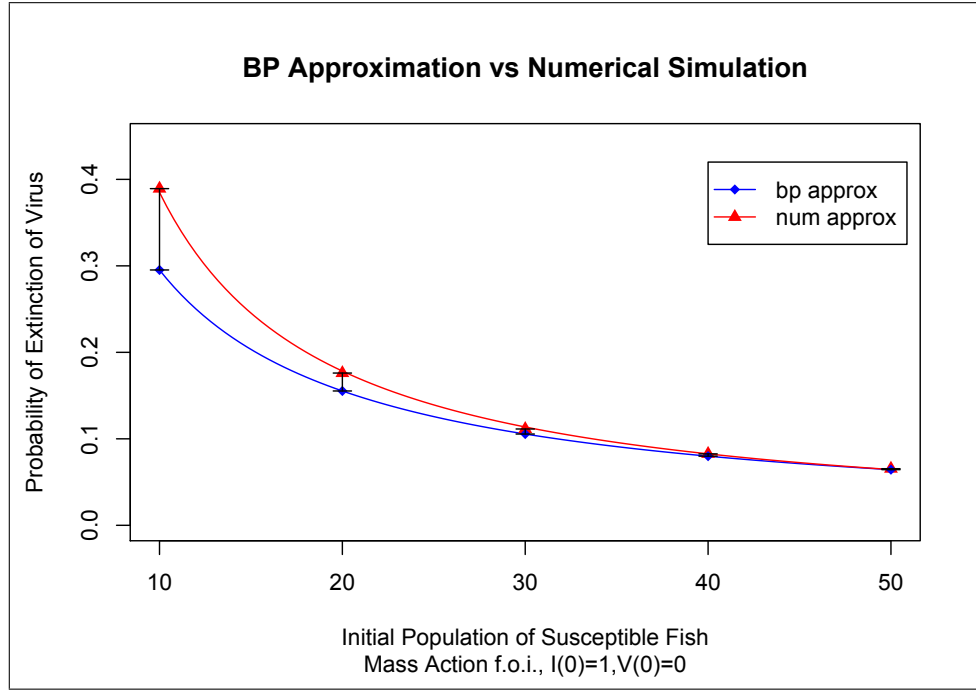


FIGURE 3. Comparison of multitype branching process approximation to numerical simulation of probability of extinction in single patch model with mass action force of infection and high mortality for infected fish. Numerical data fit with power law curve  $y = bx^{-\lambda}$  where  $b = 4.9584$  and  $\lambda = -1.11$ . Not pictured here, the absolute error was fit with a power law curve with  $b = 62.172$  and  $\lambda = -2.743$  and the relative error was fit with a power law curve with  $b = 0.4584$  and  $\lambda = -0.067$ .

ratio of realizations that reach extinction before reaching outbreak to the number that reach outbreak before extinction. Outbreak is estimated by endemic equilibrium of the associated deterministic system.

Under the assumption that a random variable is normally distributed, the law of large numbers indicates that the error in numerical estimate of a probability using  $1 \times 10^6$  trials is 0.001. In Table 7, the difference between numerical and branching process approximation

Init. Pop.	$f_1, \alpha = 3.3$	$f_2, \alpha = 3.3$	$f_1, \alpha = 1.5$
10	0.094	0.245	0.056
20	0.021	0.025	0.009
30	0.006	0.003	0.003
40	0.003	0.002	0.001
50	0.001	0.001	0.000

TABLE 7. Entries represent absolute error between numerical results and multitype branching process results. Mass action force of infection is represented by  $f_1$  and Monod *f.o.i.* is represented by  $f_2$ . High infected mortality is represented by  $\alpha = 3.3$  and low by  $\alpha = 1.5$ .

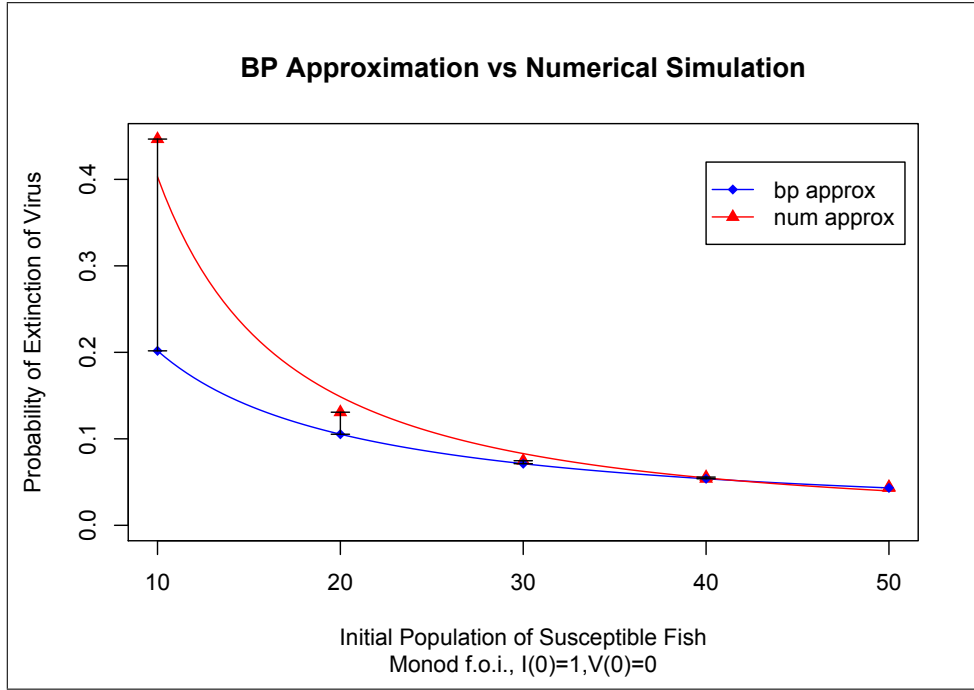


FIGURE 4. Comparison of multitype branching process approximation to numerical simulation of probability of extinction in single patch model with Monod force of infection and high mortality for infected fish. Numerical data fit with power law curve  $y = bx^\lambda$  where  $b = 11.074$  and  $\lambda = -1.439$ . Not pictured here, the absolute error was fit with a power law curve with  $b = 756.67$  and  $\lambda = -3.507$  and the relative error was fit with a power law curve with  $b = 68.329$  and  $\lambda = -2.068$ .

is reported for the three scenarios described above. Once the branching process approximation is within 0.001 of the numerical estimate, it is within 0.002 of the true probability.

## 6. CONCLUSIONS

The outbreak of Infectious Salmon Anemia virus in one and two patches is modeled using deterministic and stochastic techniques. Analysis of deterministic models indicates that if  $\mathcal{R}_0 > 1$ , the virus persists whenever it is introduced. However, when the number of individuals in infected classes are few, the mean field assumption underlying differential equation models is invalid. When random fluctuations influence the dynamics of the system, it is always possible for the virus to go extinct. In each of the numerical simulations reported in Sections 2-4, the basic reproduction number is much greater than the threshold value of 1. Never-the-less, the probability of extinction is greater than zero, regardless of the approximation method. In many cases, multitype BGWbp models can provide an analytic estimate for the probability of extinction. Even when they cannot provide an analytical result, iteration of the probability generating function converges to this probability after only a few iterates.

Multitype branching processes prove to be an useful tool to derive approximations of the probability of extinction in the CTMC model of disease outbreak. The approximation's accuracy is reliant on the size of the initial size of susceptible individuals exceeding

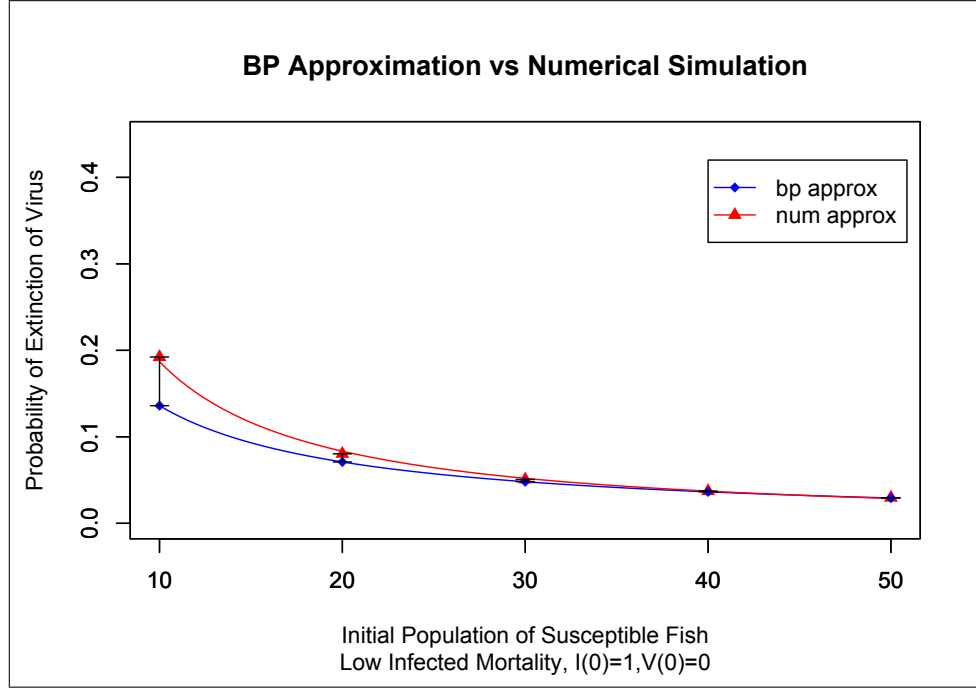


FIGURE 5. Comparison of multitype branching process approximation to numerical simulation of probability of extinction in single patch model with mass action force of infection and low mortality for infected fish. Numerical data fit with power law curve  $y = bx^\lambda$  where  $b = 2.7264$  and  $\lambda = -1.164$ . Not pictured here, the absolute error was fit with a power law curve with  $b = 42.109$  and  $\lambda = -2.847$  and the relative error was fit with a power law curve with  $b = 14.459$  and  $\lambda = -1.659$ .

some critical population size. In the absence of analytical tools to predict this critical size, the accuracy of branching process approximations have been estimated by comparison to numerical simulations of the CTMC model.

In Section 5, it is clear that changes to the transition probabilities result in changes to the critical population size for accurate branching process approximation. It was already noted that the probability of extinction is greater than zero whenever  $\mathcal{R}_0 > 1$ , even when it is much greater than 1. Table 7 reports the absolute error between the numerical estimate and the branching process estimate. It illustrates that the accuracy of the branching process approximation depends on the transition rates in the model. This dependence is detected even though the mesh of data points is coarse. The power law fitting of the absolute and relative errors for each of the three scenarios shows that the error is converging to zero, but also that the rate of convergence varies among them.

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